REMARKS

Formal Matters

Claims 29-30, 36-40, 46-49, 52-54 are currently pending in this application. No amendments have been made to the claims.

35 U.S.C. § 103(a)

The Office Action maintains the rejection of claims 29, 30, 36-40, 46-49 and 52-54 under 35 U.S.C. § 103(a) as allegedly being obvious over Motoyama *et al.*, (1998) *Nat. Genet.* 18(2): 104-106 ("Motoyama") in view of U.S. Patent No. 5,932,448 to Tso *et al.* ("Tso").

The Office action reasons that a pool of antibodies generated against mouse Patched-2 would inherently contain antibodies which would also bind human Patched-2 because the Patched-2 proteins are 89.3% similar, and contain regions in which there are at least 5-7 amino acid identities (the approximate length of amino acids contained in an epitope). The Office Action further states that as the Specification does not define "specifically bind" to exclude the binding of an antibody to an epitope on one protein and not the same epitope on another protein, the term does not exclude the antibodies from binding human Patched-2 as well as mouse Patched-2. Therefore, the Office Action rejects the claims under 35 U.S.C. § 103(a) over Motoyama (which teaches the amino acid sequence of mouse Patched-2) in view of Tso (for teaching production of antibodies, including bispecific antibodies), stating that it would be obvious to produce antibodies against mouse Patched-2 by using the method of Tso. Such antibodies would inherently (always and inevitably) contain antibodies that also bind to human Patched-2.

Phrased another way, the argument is that mouse Patched-2 was known. Motoyama did not make antibodies that specifically bound to mouse Patched-2, however, *if* Motoyama made antibodies against Patched-2 using the method of Tso, then such antibodies would inevitably and

always contain antibodies that would also specifically bind to the unknown human Patched-2 homolog (if it in fact existed).

The Examiner has failed to cite any reference showing antibodies that bind Patched-2. Anticipation is a doctrine that states that the claimed subject matter was known in the prior art, not that the claimed subject matter *could have been known* in the prior art through the combination of various teachings. In the instant Office Action, the argument is that although Motoyama did not make any antibodies against the mouse Patched-2, he *could have*, using the method of Tso, and *if he had* made such antibodies, these would also bind the yet undiscovered and uncharacterized human Patched-2 homolog. This reasoning stretches the Doctrine of Inherent Anticipation beyond its intended boundaries. The Doctrine of Inherent Anticipation was devised address anticipation by something that existed in the prior art, but may have been unrecognized, not to address anticipation by something that *could have been* in the prior art through a combination of references.

In the instant case, the Examiner has not pointed to any reference describing monoclonal antibodies against any Patched-2 protein. Instead the Examiner has combined a teaching of the Patched-2 protein with a general method of making antibodies to state that antibodies against the mouse Patched-2 are obvious. Then the Examiner extends this to state that such a theoretical pool of antibodies would inevitably and always contain antibodies that also specifically bound human Patched-2 protein (despite the fact that no such protein was ever described prior to the Applicants' disclosure).

The Examiner's reliance on a general teaching that epitopes are 5-7 amino acids and therefore, any finding of the same 5-7 amino acids on two different proteins means that the two proteins contain the same "epitope," is misplaced. First, not all such amino acid groupings constitute epitopes in practice:

> Although, in theory, each 4-8 residues can constitute a separate antigenic determinant, in practice, the number of antigenic determinants per antigen is much lower than what would theoretically be possible. Usually the antigenic

> determinants are limited to those portions of the antigen that are accessible to antibodies….
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> Mayer IMMUNOLOGY; Chapter 3 "Antigens," Microbiology & Immunology Online, Univ. South Carolina School of Medicine (2009) (http://pathmicro.med.sc.edu/mayer/antigens2000.htm)

Proteins are three-dimensional structures, so not all groupings of amino acids may be accessed by the antibodies such that binding occurs and such amino acid grouping is an "epitope." Further, "epitopes" may be linear stretches of amino acids ("linear epitopes"), or may be a cluster of non-contiguous amino acids ("conformational epitopes). These groupings of 5-7 amino acids in length or cluster may not be immunogenic, and therefore, would not constitute an "epitope." The lack of immunogenicity of certain amino acid groupings may be explained by several factors:

> Many factors influence the immunogenicity of proteins, including structural features (sequence variation and glycosylation), storage conditions (denaturation, or aggregation caused by oxidation), contaminants or impurities in the preparation, dose and length of treatment, as well as the route of administration, appropriate formulation and the genetic characteristics of patients.
>
> Schellenkens, H. (2005) *Nephrol. Dial. Transplant.* 20 (Suppl. 6) vi3-vi9 (copy attached)

Thus, such features as hydrophobicity of the amino acid groupings, tolerance, inaccessibility in the protein, whether reduced or non-reduced material is used for immunizations, and the genetic background of the animal used for immunization (which may or may not have the necessary repertoire of immunoglobulin genes to form antibodies that recognize such an amino acid grouping (or the necessary repertoire of T-cell receptors that produce the necessary T_H cells)) all potentially play a role in whether a given amino acid grouping is an "epitope."

It is also simply not true that a polyclonal serum may be generated in an animal against a given protein and will inevitably and always have cross-reactivity to the homologous protein of another species. Surman, D.R., *et al.* (1998) *J. Immunol. Methods* 214(1-2):51-62 ("Surman")

(copy attached for the Examiner's convenience), showed that immunization of rabbits with nucleic acid encoding mouse tyrosinase (TRP-1) generated anti-mouse tyrosinase polyclonal serum that failed to react with human tyrosinase despite a 81% homology between human and mouse tyrosinase (Surman at p. 60, bottom of first column). Surman is an example of how this area of immunology can be unpredictable and immunization to of animals to obtain antibodies against a protein may produce specific polyclonal antiserum that does not contain antibodies that recognize the homologous protein of another species.

Surman is evidence that the Examiner's argument that immunization to generate antisera against mouse Patched-2 would inevitably and always generate antibodies that also recognized human Patched-2 is flawed, and cannot support a finding of "inherent anticipation." The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." (*In re Robertson*, 169 F.3d 743, 745, 49 USPQ2nd 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

Reconsideration and prompt allowance of the claims is respectfully requested.

SUMMARY

Claims 29, 30, 36-40, 46, 49 and 52-54 are pending in the application. Applicants respectfully request reconsideration and allowance of the claims.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is strongly encouraged to call the undersigned at the number indicated below.

This response is submitted with a Petition for a one-month extension of time, Request for Continued Examination and requisite fees. However, in the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request allowance of the claims as presented herein.

Respectfully submitted,
GENENTECH, INC.

Date: March 9, 2010 By: /Patrick J. Farley/

Patrick J. Farley, Ph.D.
Reg. No. 42,524
Telephone No. (650) 467-3618